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Food for thought: The role of nutrition in the microbiota-gut–brain axis

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SUMMARY

Recent research has provided strong evidence for the role of the commensal gut microbiota in brain function and behaviour. Many potential pathways are involved in this bidirectional communication between the gut microbiota and the brain such as immune mechanisms, the vagus nerve and microbial neurometabolite production. Dysbiosis of gut microbial function has been associated with behavioural and neurophysical deficits, therefore research focused on developing novel therapeutic strategies to treat psychiatric disorders by targeting the gut microbiota is rapidly growing. Numerous factors can influence the gut microbiota composition such as health status, mode of birth delivery and genetics, but diet is considered among the most crucial factors impacting on the human gut microbiota from infancy to old age. Thus, dietary interventions may have the potential to modulate psychiatric symptoms associated with gut–brain axis dysfunction. Further clinical and *in vivo* studies are needed to better understand the mechanisms underlying the link between nutrition, gut microbiota and control of behaviour and mental health.

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1. Introduction

The microbial population residing in the small and large intestine represents the largest microbial population of the human microbiota. Estimates suggest that bacterial cells within the gut microbiota outnumber human eukaryotic cells by ten to one [1]. Moreover, the genes encoded by the gut microbiota, the gut microbiome, outnumber the human genome by one hundred to one [2]. This complex ecosystem is formed mainly by bacteria, but also viruses, archae, protozoa and fungi. Due to the advances in genomic technologies it has been possible to unravel around 75% of the adult gut microbiota bacterial composition, which is predominantly composed of the Firmicutes and Bacteroidetes phyla [3].

Furthermore, the gut microbiota plays a major role in host health by shaping the development of the immune system, metabolizing dietary nutrients (such as fatty acids, glucose and bile acids) and drugs, digesting complex indigestible polysaccharides and synthesizing vitamins and bioactive molecules [4].

Throughout different life stages, various changes occur in the microbial diversity of humans. Early studies suggested that the foetus first came in contact with microbes during birth. However, it has been posited that as early as the prenatal period, an initial inoculum of microbes may be translocated via the bloodstream and placenta from the mother to the foetus, thus contradicting the “sterile womb” hypothesis [5].

After birth, the first colonizers of the gut are facultative anaerobes such as *Streptococcus*, *Enterobacteriaceae* and *Staphylococcus*. These colonizers consume oxygen, creating an anaerobic environment leading to an increase of *Clostridium*, *Bacteroides* and *Bifidobacteria*, which are strict anaerobes. During this early post-natal period, diet (breast milk/formula feeding) plays a key role in shaping the gut microbiota composition [6]. This unstable infant gut microbiota with low diversity goes through a number of compositional changes during the first two years of life. From the second year of life onward, the microbial composition undergoes an important shift toward the stable gut microbiota profile of the adult, which is composed mainly of *Bacteroidetes* and *Firmicutes*. During healthy adulthood the gut microbiota remains relatively stable until ageing, when considerable changes occur [7].

The intestinal microbes are markedly affected by numerous factors such as host genetics, mode of delivery, lifestyle (urbanization and global mobility), medical interventions (use of antibiotics, vaccinations and hygiene) and health status [8]. Furthermore, diet has repeatedly shown to be one of the most important factors affecting gut microbiota establishment and composition throughout the lifespan [4]. Indeed, more than 50% of the variation of gut microbiota has been related to dietary changes [9] and major changes in diet during adulthood can modify the microbiota in a matter of days [10].

Furthermore, an alteration of gut microbiota and metabolism, through dietary or other environmental influences, can cause a state of dysbiosis, which is characterized by an overgrowth of potentially pathogenic organisms (pathobionts) [11]. This change in the balance of symbionts/pathobionts can induce reduced intestinal barrier function (leaky gut) and subsequent chronic inflammation. Such dysbiosis may be associated to some metabolic and inflammatory disorders, visceral pain and even alterations to central nervous system (CNS) functioning [12,13]. Hence the relationship between the gut microbiota, chronic inflammation and the CNS suggest that microbial dysbiosis could alter brain function and hence contribute to behavioural and cognitive abnormalities [14]. A wealth of preclinical research is now showing potential for the treatment of dysbiosis, through dietary measures, to improve cognitive and behavioural outcomes.

Given such evidence, there is a growing appreciation for the importance of the gut microbiota in health and disease, including mental health. Bearing in mind that diet is one of the most crucial factors in the development of the human gut microbiota from infancy to old age, this review focuses on the role of the gut–brain axis in brain function and behaviour and the potential nutritional interventions to target this axis as psychiatric disease therapies.

2. How does diet influence human microbiota?

The human gut harbours over ten thousand species of microorganisms [15], hence such taxonomic diversity requires a wide array of nutrients and energy sources for normal microbial growth and function. Narrowing of host dietary diversity and reduced intake of essential nutrients can therefore reduce availability of substrates for specific microbial growth and contribute to intestinal dysbiosis.

Over recent decades, modern dietary patterns have undergone major compositional changes, with increased intakes of red meat, high fat foods, and refined sugars. This 'Westernization' of diets together with sedentary lifestyles results in modifications to the gut microbiota, which may partially contribute to the higher incidences of chronic inflammatory disorders, such as cardiovascular disease, obesity, depression, allergies, diabetes and autoimmune disorders [16]. It is therefore clear that in order to improve the nutritional value of food and thus, human health, it is essential to understand the biological interactions between the diet and microbiota.

Many human studies have assessed dietary impact on the gut microbiota. However, as is the case with many human studies, they are limited by the difficulties to control potential confounding variables such as habitual diets and lifestyle behaviours. Moreover, it is worth noting that, typically, sequencing of the human gut microbiota is carried out on faecal samples, which may not accurately reflect the microbiota composition of the different intestinal segments. Despite these limitations, much of this human data is useful to assess the role of varying dietary patterns on microbiota composition and function.

2.1. Rural vs western diet

Many studies comparing rural and western communities have revealed specific gut microbiota adaptations to their respective environments. The adaptations to westernization have resulted in an important loss of several bacterial species, and hence subsequent reduction in microbial diversity and stability. Recent studies have clearly showed this reduction in microbiota diversity such as the one comparing an Italian urban control group compared to a hunter–gatherer community [17]. Moreover, recent investigations have reported the impact of diet on the microbial biodiversity within different human populations [18]. African children, who consume a low-fat and high-fibre diet, presented less potentially pathogenic bacteria and greater degree of diversity and microbial richness than European children consuming a high-fat diet (Western diet). African children had a depletion in *Firmicutes* and a greater abundance of the phylum *Bacteroidetes* (*Xylanibacter* and *Prevotella*), while European children showed a significant increase of *Firmicutes* (*Faecalibacterium* and *Acetitomaculum*) and *Enterobacteriaceae* (*Shigella* and *Escherichia*) [18]. Similar findings were observed in terms of an increase of *Prevotella* genus in rural African populations compared to US Americans [19].

2.2. Mediterranean diet

The Mediterranean diet is characterised by an abundance of fruits, vegetable, grains and mono-unsaturated or n-3 polyunsaturated fats. Hence it is regarded as the gold-standard for optimum health. A recent study showed the ability of a Mediterranean-inspired anti-inflammatory diet to reduce inflammation in Crohn's disease. The results demonstrated a small reduction of the acute phase protein C-reactive protein (CRP), an increase in *Bacteroidetes* and *Clostridium* clusters and a decrease in *Proteobacteria* and *Bacillaceae* population [20]. Similarly De Filippis et al. recently observed that Italian subjects with a high adherence to a Mediterranean diet had greater abundance of *Prevotella* and short chain fatty acids. Conversely, those with low adherence had higher urinary trimethylamine oxide (TMAO), which has associations with gut dysfunction, cardiovascular disease and colorectal cancer [21].

2.3. Vegetarian/vegan diets

Vegetarian diets have also gained recognition as a healthy and therapeutic dietary pattern for a number of chronic diseases, while vegan diets may confer protective benefits beyond that of vegetarian diets [22]. Vegan diets may have protective effects against metabolic and inflammatory diseases. Moreover, they appear to lead to a unique gut microbiota profile characterized by a reduction of pathobionts [22]. Some studies have shown that vegetarian and vegan diets significantly decrease microbial counts of *Bacteroides fragilis* compared to an omnivore diet [23]. Another study comparing vegetarian to omnivore diet observed a higher ratio (%) of *Bacteroides–Prevotella*, *Bacteroides thetaiotaomicron*, *Clostridium clostridioforme* and *Faecalibacterium prausnitzii* but a lower ratio (%) of the *Clostridium cluster XIVa* in vegetarian diet [24].

2.4. High-fibre diets

Numerous studies support the idea that diets rich in plant fibres may promote the diversification of the microbiota by promoting hydrolytic bacteria and stimulating the production of short chain fatty acids [18]. High-fibre diets have been positively associated with *Actinobacteria* and *Bacteroidetes* presence [25]. One study showed that three diets with different fibre-rich whole grains (barley, brown rice or combination of both) increased microbial diversity, the *Firmicutes*/*Bacteroidetes* ratio, and the abundance of the genus *Blautia* in fecal samples [26]. Furthermore, the administration of whole grain barley induced an increase in *Bifidobacteria* which is considered a positive indicator of prebiotic activity [27]. A recent study found an elevation of *Bifidobacteria* and a reduction of *Bacteroides* spp. and *Clostridium histolitycum* group in a cohort of overweight adults after administration of prebiotics (GOS) [28]. Davis et al. showed as well that an administration of GOS increased abundance of *Bifidobacteriaceae* and decreased *Bacteroidaceae* family [29].

2.5. High-fat diets

Over the last few decades, the increase in the consumption of high-fat diets has been associated with the obesity epidemic [30]. Many studies have shown that high-fat diets lead to a decrease in *Bacteroidetes* and an increase in *Firmicutes* [31]. These effects may be associated with increased gut permeability, a higher capacity for energy harvest and storage, and inflammation [31].

Several studies have focused on dietary supplementation as a possible way to attenuate the gut microbiota dysbiosis and metabolic impairments produced by high-fat diets. For example, polyphenols, conjugated linoleic acid and short chain fatty acids supplementation during high-fat diet consumption, have displayed an improvement of gut microbiota dysbiosis [32–34].

2.6. High-protein diets

The western diet has experienced a considerable increase in protein content in recent times. This has led to much research examining variations in macronutrients intake in order to manage body

weight [35]. Dietary proteins undergo luminal proteolysis and subsequent metabolism by the large intestine microbiota triggering the production of numerous amino acid-derived metabolites such as phenols, indoles, amines, sulphide, ammonia and monocarboxylic acids [36].

Dietary protein intake in humans has been associated with the *Bacteroides* enterotype [25]. An animal-based diet in humans showed an increase in the abundance of bile-tolerant microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*) and a decrease in the levels of *Firmicutes* that metabolize dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*) [10]. Interestingly, Clarke et al. showed the importance of exercise in the relationship between the microbiota, host immunity and host metabolism, and the important role played by the diet. They compared male elite professional rugby players to healthy male controls, finding a positive correlation between protein consumption with microbial diversity [37].

3. Gut-microbiota–brain communication

As previously discussed, diet significantly modifies host gut microbiota composition and function. Simultaneously, however, gut microbiota determine what the host is capable of extracting from its diet, from nutrients to bioactive signalling molecules such as neurometabolites, vitamins and short-chain fatty acids (SCFA) [38]. Many of these molecules such as serotonin and gamma-aminobutyric acid (GABA), have neuro-active functions due to their capacity to modulate neural signalling within the enteric nervous system and consequently influence brain function and host behaviour [39].

This gut–brain axis, the bidirectional communication system between the gastrointestinal system and the CNS, plays an important role in homeostasis between neural (both enteric and central nervous systems), hormonal and immunological signalling [14]. Through this complex network the gut can influence the brain via visceral messages, and conversely, the brain is able to influence gastrointestinal functions (like motility, secretion and mucin production) and immune functions, such as the modulation of cytokine production by cells of the mucosal immune system [40].

Both luminal nutrients and gut microbiota metabolites stimulate enteroendrocrine cells (EECs) located throughout the gastrointestinal (GI) tract, which represents the largest endocrine organ in the human body [41]. These EECs contain most of the nutrient receptors such as those for aminoacids, peptones, SCFAs, long-chain fatty acids (LCFAs) and oleoylethanolamide (OEA) (Fig. 1). Molecular sensing by these EEC's are crucial in the control of multiple functions during digestion, the initiation of neural and hormonal responses or changes in mucosal ion transport which controls appetite, insulin secretion and motility [42]. Moreover, as the nervous and endocrine signalling between the gut and the brain is essential for the modulation of many GI functions, the sensing receptors of the gut that control the release of many hormones play a key role (Fig. 1). Several interacting factors such as diet and microbiota composition modulate the activation of different sensory receptors in the gut, and consequently stimulate up or down-regulation of hormonal release which can induce a number of functional GI changes. Interestingly, increasing evidence indicates that animals fed on a high-fat diet present numerous changes in gastrointestinal function, particularly in the secretion and signalling of gastrointestinal hormones, which may predispose to an increase in energy intake, and consequently, to weight gain and obesity [43].

In addition to its role as a sensory organ, the gut forms part of the enteric nervous system, which makes up a comprehensive division of the autonomic nervous system, containing between 200 and 600 million neurons [42]. The vagus nerve (the major nerve of the parasympathetic division of the autonomic nervous system) is crucially involved in bidirectional signalling between the gastrointestinal and nervous systems (Fig. 2). A landmark study by Bravo et al. [44] found that probiotic modulation of the gut microbiota induced behavioural and neurochemical changes in mice. However, this was not apparent in mice that had undergone vagotomy suggesting a crucial role for the vagus nerve in the gut–brain axis.

The human intestine also acts as an endocrine organ through direct and indirect production of microbial metabolites and neurometabolites such as short chain fatty acids (SCFAs), vitamins and neurotransmitters, which have also been shown to influence gut–brain interactions [8]. GABA and serotonin are neurotransmitters that can influence host behaviour and are produced directly or indirectly by certain commensal microbes [45,46]. SCFAs including butyrate, propionate and acetate can be

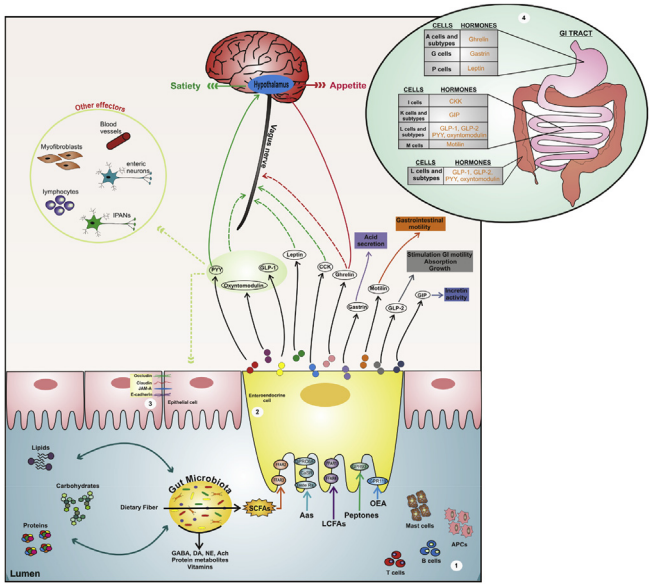

Fig. 1. Interactions between luminal nutrients and gut microbiota metabolites with the gut sensory receptors, and the key communications between endocrine, neuronal and immune systems. Dietary composition determines the type of nutrients that reach the luminal gastrointestinal tract. Different dietary patterns can alter the composition of the gut microbiota and consequently the production of their metabolites, which can influence: epithelial permeability by acting on the cells from the immune system (1), activity of enteroendocrine cells (2) or tight junction protein function (3). The gut luminal content is continuously monitored by the intestine to optimize nutrient assimilation and protect against hazards which can affect its integrity. Therefore, the intestine is conferred with a range of sensory receptors which interact with major effector systems such as the endocrine system, the nervous system, the gut immune system, and the nonimmune defence systems of the gut. Hormone release triggered by the activation of nutrient-specific receptors found on the enteroendrocrine cells, occurs along the entire gastrointestinal tract from the stomach to the large intestine. There are several types of enteroendocrine cells such as L cells or I cells with sensory receptors that stimulate the release of different types of hormones (4), which have a wide range of effects such as satiety through the hypothalamus, gastrointestinal motility and acid secretion. Abbreviations: Aas, aminoacids; Ach, acetylcholine; APCs, antigen-presenting cells; CCK, cholecystokinin; DA, dopamine; GABA, gamma-aminobutyric acid; GIP, gastric inhibitory peptide; GLP, glucagon-like peptide; IPANs, intrinsic primary afferent neuron; LCFAs, long-chain fatty acids; NE, norepinephrine; OEA, oleoylethanolamide; PYY, peptide YY; SCFAs, short-chain fatty acids.

produced by species such as *Roseburia* spp and *Faecalibacterium* following fermentation of indigestible polysaccharides [47]. Butyrate and propionate can modulate brain functioning, in particular appetite regulation and energy homeostasis [48] through regulation of neuropeptide production.

The role of the gut microbiota in immune activation also has strong associations with neurological functioning. The gut microbiota regulate intestinal epithelial barrier integrity and hence control the translocation of viable bacteria or bacterial endotoxins into the bloodstream [49]. Increased intestinal permeability can lead to increased lipopolysaccharide (LPS) in the bloodstream, which increases inflammatory status. Diet and obesity significantly alter gut microbiota composition and hence have been shown to affect inflammatory status. Cani et al. showed that prebiotic supplementation dampened inflammatory status and improved gut barrier function in genetically obese mice [50]. Many supporting studies have demonstrated the potential for high fat and other obesogenic diets to promote inflammation and microbiota-targeted interventions, such as prebiotics and probiotics to reverse inflammatory status [51]. Chronic inflammation has been linked to a number of neurological disorders including depression and dementia [52] and hence microbiota-associated chronic inflammation may influence risk of such disorders.

Due to the fact that many of these gastrointestinal pathways significantly influence neurological function, there is potential for dietary interventions that increase bacterial metabolism and promote growth of beneficial bacteria, to positively modulate the gut–brain axis and improve symptoms of

psychiatric illness. Moreover, bearing in mind the potential link between the gut microbiota and anxiety-related behaviour [8], research has recently focused on the health benefits of probiotic administration on psychiatric illnesses [53].

4. Microbiota-targeted dietary interventions and behavioural outcomes

The gut microbiota have been implicated in a number of clinical neuropsychiatric disorders [14]. Also, the role of nutrition in the aetiology and treatment of psychiatric disorders has come to light in recent times [54]. The development of next generation sequencing technologies has also allowed for increased understanding of human gut microbial composition in healthy and disease states and how environmental factors such as diet influence this composition.

4.1. Probiotic interventions

A number of studies have reported certain probiotic strains, primarily *Lactobacillus* and *Bifidobacteria*, to enhance brain function in both rodents and humans. Hence there is potential for 'psychobiotics' (live organisms that, when ingested, confer a benefit to host psychiatric health) to modulate the

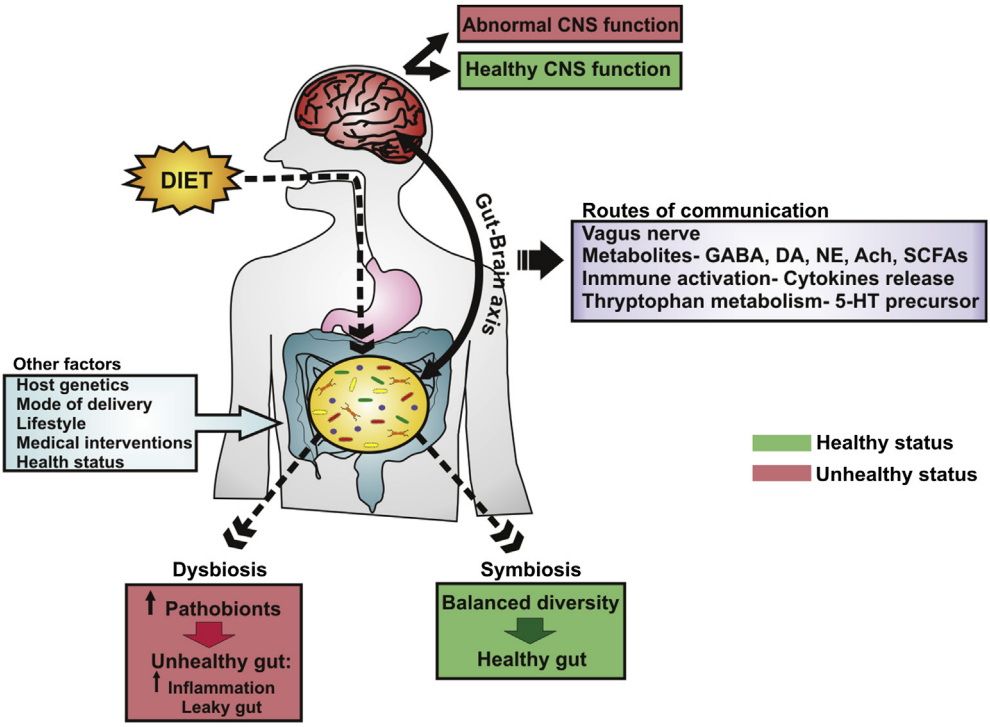

Fig. 2. Impact of diet on the gut microbiota and routes of communication involved in the gut–brain axis. Diet is one of the most crucial factors in the development of the human gut microbiota. Different dietary patterns can change the gut microbiota composition by keeping a balanced diversity of the gut microbiota (symbiosis) or causing a state of dysbiosis which is characterized by an overgrowth of potentially pathological organisms (pathobionts). A state of dysbiosis leads to an increased inflammation and leaky gut. Many mechanisms have shown to be involved in this bidirectional pathway between the gut microbiota and brain including vagus nerve signalling, immune activation, tryptophan metabolism and production of microbial metabolites and neurometabolites. Many of these bacterial metabolites significantly impact neurological function, therefore there is potential for dietary interventions that increase bacterial metabolism and promote growth of beneficial bacteria, to beneficially modulate the gut–brain axis and modulate CNS function. Abbreviations: GABA, gamma-aminobutyric acid; DA, dopamine; NE, norepinephrine; Ach, acetylcholine; SCFAs, short-chain fatty acids; 5-HT,serotonine; CNS, central nervous system.

gut microbiota and act as therapies for psychiatric disorders [53]. Table 1 summarizes a non-comprehensive list of human and preclinical studies investigating the role of probiotics in behaviours associated with psychiatric illness. Despite the promising evidence in animals, these results have yet to be fully translated into humans. However with larger randomised controlled trials, there is potential for psychobiotics to be effective psychiatric therapeutics.

4.2. Dietary interventions

Many studies have shown a clear association between the gut microbiota and behavioural alterations, and given that gut microbiota is affected by diet, the composition of the diet may be a crucial factor contributing to these behavioural changes, as summarized in Table 2.

Large macronutrient alterations as reflected in western style diets have been shown to induce microbial dysbiosis, which has been linked to impaired cognition. Magnusson et al. examined

Table 1
Probiotic interventions and behavioural outcomes.

Intervention	Species	Health status	Microbiota changes	Behavioural/neurochemical outcomes	References
Lactobacillus casei	Humans	Healthy	—	↑ mood (self reported) ↓ memory	[66]
Bifidobacteria longum	Mice	Healthy anxious strain (BALB/c)	—	↑ memory and cognitive performance (novel object recognition, barnes maze, fear conditioning)	[67]
VSL#3	Rats	Aged	↑ *Bacteroidetes*	↓ deficit in age-related LTP ↓ microglial activation ↑ BDNF and synapsin	[68]
Lactobacillus helveticus	Mice	Healthy or fed western-diet	Normalized the increase in *Proteobacteria* following "western diet" feeding	↑ memory (Barnes maze) ↓ anxiety-like behaviour (Barnes maze)	[59]
Bacteroides fragilis	Mice	MIA treated	Restored relative abundance of *lachnospiraceae* following MIA treatment	↓ anxiety-like behaviour (Open field) ↑ communication (ultrasonic vocalization) ↓ stereotyped behaviour (marble burying)	[69]
Lactobacillus casei	Humans	Chronic fatigue syndrome	↑ *Bifidobacteria* ↑ *Lactobacillus*	↓ anxiety	[70]
Lactobacillus helveticus and *Bifidobacterium longum*	Rats	Healthy	—	↓ anxiety (conditioned defensive burying)	[71]
	Humans	Healthy	—	↓ anxiety	
Bifidobacteria infantis	Rats	Healthy	—	↓ proinflammatory immune response ↑ tryptophan	[72]
Lactobacillus rhamnosus and *Bifidobacterium animalis*	Humans	Schizophrenic	Microbiota data not reported however probiotic group significantly less likely to experience severe bowel difficulty	No observed differences	[73]
Bifidobacterium infantis	Rats	Healthy normosensitive (Sprague–Dawley) and healthy hypersensitive (Wistar–Kyoto)	—	↓ visceral pain (colorectal distension)	[74]
Lactobacillus rhamnosus	Mice	Healthy anxious strain (BALB/C)	—	↓ corticosterone, anxiety behaviour, depressive behaviour. Altered GABA receptor expression	[44]

Abbreviations: MIA, maternal immune activation; LTP, long-term potentiation; GABA, gamma-aminobutyric acid.

Table 2
Microbiota-targeted dietary interventions and behavioural outcomes.

Diet	Species	Intervention length	Microbiota changes	Behavioural outcomes	Biochemical outcomes (possible mechanisms)	References
High-fat diet	Mice	13 weeks	↑ *Firmicutes* (mainly *Ruminococcaceae* and *Lachnospiraceae*) ↓ *Bacteroidetes (S24-7)*	↓ Burrowing (Burrowing Test) ↓ Memory (Morris water maze test)	No difference between diet groups was observed for sucrose preferences, LPS, cholesterol, HbA1c, BDNF and the cytokines IL-1α, IL-1β, IL-6, IL-10, IL-12(p70), IL-17 and TNF-α. Low-grade levels of the systemic inflammatory mediators IL-6, IL-12p70 and IL-17A correlated to memory, anxiety, anhedonia and species-typical behaviour	[56]
High-fat diet	Mice	2–5 weeks	↑ *Clostridiales* and *Erysipelotrichales* ↓ *Bacteroides*	No significant differences from the control mice, except for remaining focused on the old platform position during the reversal probe trial	—	[55]
High-sucrose diet	Mice	2–5 weeks	↑ *Clostridiales*, *Lactobacillus* (*Enterococcus*, *Lactococcus* and *Lactobacillus*) and *Lactococcus* ↓ *Bacteroides*	↓ Learning (Morris water maze test) Cognitive deficits (in spatial short-term memory) Impairments in early development of a spatial bias for long-term memory, short-term memory and reversal training, compared to mice on normal diet	—	[55]
MgD diet	Mice	6 weeks	Principal Component Analysis plots illustrating differences in GM composition. The GM profile of MgD mice differed significantly from mice fed a standard control diet	↑ FST – Increased immobility (depressive-like phenotype)	Strong tendency towards decreased mRNA IL-6 levels in the MgD mice. The GM of MgD mice correlated significantly to hippocampal IL-6 levels	[61]
MgD diet	Mice	6 weeks	↓ Bacterial diversity of the gut Principal component analysis plots illustrating differences in GM composition between mice fed a control diet or an MgD diet	Altered anxiety-like behaviour (↓ Latency to enter the light compartment in the Light Dark Box test)	—	[62]

(*continued on next page*)

Table 2 (*continued*)

Diet	Species	Intervention length	Microbiota changes	Behavioural outcomes	Biochemical outcomes (possible mechanisms)	References
Meat-containing diets	Mice	3 months	↑ Bacterial diversity	↑ Working and reference (temporary and long-term) memory. ↓ Anxiety-like behaviour	—	[57]
Western-style diet high in fat	Mice	21 days	↑ *Firmicutes*/*Bacteroidetes* ratio ↑ Abundance of *Proteobacteria* and *Spirochaetes*	Altered anxiety-like behaviour	↓ total levels of SCFAs in cecal contents ↓ levels of acetic, propionic and butyric acids ↑ levels of caproic acid	[59]
High-fat diet (fecal transplantation from donors on high-fat diet)	Mice	10 weeks	Sequencing-based phylogenetic analysis confirmed the presence of distinct core microbiota between groups, with alterations in α- and β-diversity, modulation in taxonomic distribution, and statistically significant alterations to metabolically active taxa	Disrupted exploratory, cognitive, and stereotypical behaviour	Disrupted markers of intestinal barrier function ↑ circulating endotoxin ↑ lymphocyte expression of ionized calcium-binding adapter molecule 1 ↑ toll-like receptor 2 ↑ toll-like receptor 4	[58]
High-fat diet	Mice	8 weeks	↑ *Firmicutes* ↓ *Bacteroidetes* and *Tenericutes*	Robust anxiety phenotype	—	[60]
Diet supplemented with prebiotics (trans-GOS)	Human	8 weeks	Enhanced *Bifidobacteria*	Improved anxiety (HAD scale)	—	[65]

Abbreviations: HAD, Hospital Anxiety and Depression scale; SCFAs, short-chain fatty acids; GM, gut microbiota; LPS, Lipopolysaccharide; HbA1c, hemoglobin A1c; BDNF, brain-derived neurotrophic factor; trans-GOS, trans-galactooligosaccharides; MgD diet, diet deficient in Magnesium.

microbiota compositional changes following high fat, high sucrose or standard chow diets and assessed associations with cognitive capabilities in mice [55]. *Lactobacillus* was significantly increased in the high sucrose group whereas *Erysipelotrichales* was significantly increased in the high fat group. High fat and high sucrose both had increased *Coriobacteriales* and reduced *Bacteroides.* Both high-energy treatments induced impaired cognition in the Morris water-maze and step-down latency tasks. In addition these behavioural changes displayed significant correlations with the alterations in *Lactobacillus*, *Erysipelotrichales*, *Coriobacteriales* and *Bacteroides.* These results suggest that the cognitive changes induced by the western-style diets are mediated through alterations to the gut microbiota. Jørgensen et al. performed a similar study with the same treatment groups and found similar correlations between microbiota alteration and memory which was also associated with inflammatory status [56].

Li et al. also reported diet-induced changes to microbial diversity to improve cognition and working memory in mice. In this study, a meat-containing diet led to greater gut microbiota diversity than found in the control diet group. Moreover, the meat-containing diet group had improved working and reference memory on the hole-board open field test and less anxiety-like behaviour, assessed during the novel encounter in the hole-board open field [57].

Mental decline is increased by obesity, which may be in part regulated by gut microbiota dysbiosis. A recent study showed that an obese-type microbiota, induced by high-fat feeding, induced cognitive

disruptions when transplanted into healthy rodents [58]. The high-fat diet microbiota led to a significant increase of anxiety-like behaviour in the elevated plus maze, open field, and marble burying test. Moreover, this transfer of the high-fat diet microbiota decreased the cued fear memory in comparison to mice that received microbiota from chow-fed mice. Furthermore, inflammatory markers in the medial prefrontal cortex and intestinal permeability were increased in the mice who received the high-fat diet microbiota, suggesting that immune signalling pathways may be key mediators of microbiota–brain communication. These interesting results revealed that even in the absence of obesity, an obese-type microbiota profile could induce behaviour deficits similar to those seen in obesity and hence suggesting the potential for microbiota-based dietary interventions to treat obese-associated psychiatric disorders.

In addition, Ohland et al. reported a western-style diet to induce anxiety-like behaviour in mice, as assessed in the Barnes maze [59]. Moreover, western-style diet feeding increased the *Firmicutes*/*Bacteroidetes* ratio, and the abundance of *Proteobacteria* and *Spirochaetes* as well as reducing total SCFA contents. This increased anxiety-like behaviour was not apparent in mice who had been fed a western-style diet supplemented with the probiotic *Lactobacillus helveticus*.

Another study found that mice on a high-fat diet presented major shifts in the gut microbiota (increase of *Firmicutes* and decrease of *Bacteroidetes* and *Tenericutes*) and a robust anxiety phenotype [60].

A diet deficient in Mg, increased depressive-like behaviour and altered the gut microbiota, which suggested that magnesium deficiency could be a mediator of the behavioural effects through an altered gut microbiota [61]. Interestingly, a significant correlation was found between the gut microbiota of the diet deficient in Mg and a decrease in hippocampal IL-6 levels, suggesting that this immune-modulation could be the mechanism by which diet induced changes in the gut microbiota composition alter behaviour [61]. A similar study found that a diet deficient in Mg decreased bacterial diversity and altered anxiety-like behaviour [62].

Certain prebiotics have the potential to influence central nervous system functioning through stimulation of specific microbial growth and production of SCFAs. Tarr et al. reported that a social disruption stressor significantly altered gut microbiota composition in mice, which resulted in anxiety-like behaviour and a reduction in the growth of neurons in the denate gyrus region of the hippocampus [63]. Interestingly, supplementation of the human milk oligosaccharides 3′ Sialyllactose or 6′ Sialyllactose, which have anti-inflammatory properties and stimulate bifidobacterial growth, prevented the stressor-induced alterations to the gut microbiota, in addition to preventing the behavioural, microbial and neurophysical defects [63].

A number of small clinical controlled trials have assessed the efficacy of certain prebiotics on psychological outcomes with promising results. Schmidt et al. demonstrated that 3-week supplementation with a GOS prebiotic, which has been shown to stimulate bifidobacterial growth, in healthy volunteers significantly reduced waking cortisol response, a stress hormone strongly linked to anxiety and depression [64]. Moreover, a Bimuno®-galactooligosaccharides (B-GOS) cohort demonstrated altered behavioural outcomes through a decrease in attentional vigilance to negative versus positive information in a dot-probe task compared to placebo. It is interesting to note, however, that fructooligosaccharide (FOS) supplementation had no effect. These results suggest that shaping of microbiota composition through prebiotic intake could influence behavioural outcomes [64]. In humans, prebiotic supplementation with trans-galactooligosaccharides (trans-GOS) not only enhanced bifidobacterial growth and improved bloating symptoms, but in addition significantly reduced anxiety scores in IBS sufferers [65].

5. Conclusions and future implications

It is evident that there are a number of major metabolic, endocrine and neural pathways connecting the gut and the brain. Indeed, the trillions of microbes and microbial by-products within the gut contribute to the plasticity of these pathways. Despite the rapid growth of this area of research, it is still in its infancy. Relatively little is known about the extent to which bacterial metabolites can influence brain function, something which could be addressed with further advances in metabolomic technologies. In addition, the complexity of the pathways involved in the gut–brain axis contributes to the

difficulty of identifying true mechanisms of action. Moreover, the role of individual nutrients to affect signalling within these pathways requires further examination.

Sequencing technologies have grown extensively in recent times allowing deeper insight into gut microbial composition and associations between altered microbiota and psychiatric illnesses. Further research in this field should address mechanistic evidence for gut microbiota to alter brain and behaviour. The majority of the data available, is preclinical and few of these promising studies have been translated into humans, which warrants the need for more clinical trials in the area. There are very little data reporting clinical interventions targeting the microbiota in psychiatric illness.

Indeed, diet has a significant impact on the microbiota and hence dietary interventions can beneficially modulate microbial diversity and function. Caution must be taken on assigning the term 'probiotic' to a specific strain of bacteria until its health effects can be replicated in both humans and animals. Indeed, commercial availability of true 'psychobiotics' (a live bacteria that may benefit mental health) will only become apparent after rigorous human trials. Prebiotics and other larger dietary interventions, including dietary fats and polyphenols also pose potential to alter the gut–brain axis and hence neuropsychiatric disorders, and may be feasible as long-term interventions for mental health.

In conclusion, diet-induced gut microbiota modifications may be associated with brain dysfunction, behavioural and metabolic deficiencies. The emerging evidence of a microbiota-gut–brain axis dysregulation in certain neuropsychiatric disorders warrants further clinical and *in vivo* studies to investigate gut microbiota-targeted interventions as novel therapeutic strategies. Indeed, dietary interventions to treat dysfunction of the gut–brain axis may pose potential as therapeutic strategies for psychiatric disorders.

Conflict of interest

None.

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